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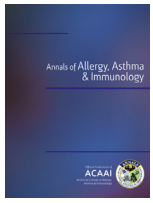

Review Article

Therapy of chronic urticaria: a simple, modern approach

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ABSTRACT

Objective: To examine the available treatment choices for chronic spontaneous urticaria (CSU) and discuss a new paradigm for treating such patients.

Data Sources: The literature regarding treatment is reviewed, including considerations of published guidelines. Attention is focused on the most recent evidence indicating particular efficacy of omalizumab.

Results: Omalizumab has been found to have considerable efficacy in phase 2 and phase 3 trials in which more than 900 patients have been studied. A response rate of 65% is seen in patients resistant to antihistamines as well as to histamine$_2$ blockers and leukotriene antagonists, and 40% of patients are completely free of hives as long as therapy is continued. In addition, serious adverse events have not been seen. Only cyclosporine can match this response rate (excluding steroids), but the adverse effect profile (blood pressure and renal function) is substantial by comparison. Double-blind, placebo-controlled studies of other agents often listed as alternatives are lacking (ie, whether their success rate exceeds the 25%-30% placebo response is uncertain). The mechanism by which omalizumab works in CSU is not clear because the response rate is unrelated to the autoimmune profile and can occur rapidly (ie, within a few days).

Conclusion: Omalizumab has exceptional efficacy for antihistamine-resistant CSU with an excellent adverse effect profile.

Introduction

Chronic spontaneous urticaria (CSU) is a disorder with a dubious reputation. It can be difficult to diagnose because exogenous causes are often suspected when none are present. Its pathogenesis is understood to some degree, but our understanding of the underlying mechanism is certainly incomplete, and there is no unanimity in the literature regarding operative molecular mechanisms. Furthermore it is generally considered to be a disease that is difficult to treat; however, new effective therapies have been identified that simplify the choices traditionally considered, and new guidelines for treatment are currently in press. In this review, I address the issues that are being considered and debated currently regarding CSU, including what to call it, how to diagnose it, what the cause is, and how to treat it. There is special emphasis on therapy that includes the newest results of drug trials and focuses on early use of agents with the greatest efficacy.

What's in a Name?

Is it *chronic urticaria*, *chronic idiopathic urticaria*, or *chronic spontaneous urticaria*? The term *chronic urticaria* has been used by many authors for decades and has led to considerable confusion. The term *chronic*, as opposed to *acute*, indicates that urticaria is present for more than 6 weeks,[1] whereas acute urticaria ceases (remits) in less than 6 weeks regardless of cause. This distinction works because most acute urticaria caused by food allergy, drug reactions, or intercurrent viral illnesses are gone within this period, assuming the offending substance is identified and/or eliminated. This definition of *chronic*, however, includes physical urticaria, such as cold urticaria, cholinergic urticaria, and dermatographism, where symptoms can be present for months or years but are induced by stimuli, such as contact with cold objects, exercise so that core body temperature is raised, or scratching the skin. It also includes the much larger population of patients with persistent hives of unknown cause that are not inducible in a reproducible fashion (ie, are not a physically induced urticaria) and whose pathogenesis and therapy are different. By considering these together, we see statements indicating that the cause of chronic urticaria is known in approximately 25% of patients. In reality, this refers primarily to those with physically inducible urticarias and confuses the word *cause* (ie, knowing how to precipitate an urticarial episode) with *etiology* (ie, why the person has hives at all). Thus, if we separate *inducible urticarias* as suggested[2] from *spontaneous urticarias*, then the cause of the spontaneous urticarias approaches zero because the etiology is not known even though there is an association with autoimmunity in approximately 45% of patients. Nevertheless, considerable progress regarding pathogenesis has been made. An alternative term for this group, *chronic idiopathic urticaria*, has also been used for years[3] and emphasizes

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that its cause and pathogenesis are unknown. However, progress has been made, and the term *spontaneous* rather than *idiopathic* emphasizes that it is endogenous rather than exogenous and noninducible rather than inducible. Thus, I support the suggestion that this disorder be named *chronic spontaneous urticaria*[4] and will refer to it as CSU in the remainder of this article.

Diagnosis of CSU

Assuming the duration has exceeded 6 weeks, the urticarial reaction associated with this disorder can be described as follows. The lesions are pruritic, red, and well circumscribed and can occur on any part of the body. They can vary in size from a few millimeters to giant hives 8 to 15 cm in diameter. They are always raised. Individual lesions last more than 4 hours but rarely more than 24 hours and disappear without leaving any mark. If there is bruising, associated petechiae or purpura, or duration that approaches 36 hours or more, a vasculitis should be suspected and a skin biopsy becomes requisite. There is no blister formation. The presence of blisters suggests eczema, erythema multiforme, or other bullous disorders.

By contrast, physically inducible urticarias, including cold urticaria, cholinergic urticaria, dermatographism, solar urticaria, local heat urticaria, and aquagenic urticaria, produce lesions that last no more than 2 hours after the stimulus is removed. The sole exception is delayed pressure urticaria, which shares characteristics of the urticarial lesions seen with CSU except that the stimulus[5] is identifiable.

There are subtle considerations where these disorders may appear to overlap. A patient with severe dermatographism, for example, may feel that the lesions are appearing spontaneously. Some patients can be so sensitive that their clothing rubbing on the skin while they are walking causes itch and hive formation. However, this is not truly spontaneous, and the circumstances need to be distinguished. In the opposite fashion, patients with CSU can have associated symptoms that are also inducible, such as pressure urticaria and dermatographism. The dermatographism is usually mild (much less intense than is seen in the typical patient whose sole problem is dermatographism), but the pressure-induced symptoms can be significant. The presence of any other inducible urticaria in a patient with CSU is a chance occurrence that is uncommon.

Approximately 40% to 50% of patients with CSU have episodes of angioedema, such as swelling of the lips, periorbital swelling, tongue swelling, or swelling of the hands, feet, and genitalia.[1,3] Whereas urticaria is due to an increase in vascular permeability in the superficial dermis, angioedema can have the same pathogenic mechanism operative in the deep dermis and subcutaneous tissue. Angioedema lasts longer than hives and may take up to 3 days to disappear completely. It is less pruritic than hives because there are fewer nerve endings mediating itch[6] in the deeper layers of the skin.

A skin biopsy is usually not requisite to diagnose CSU but is performed when the diagnosis is not clear or when a vasculitis is suspected or at least needs to be ruled out. There are no laboratory tests absolutely requisite to make the diagnosis and guidelines available may not be identical,[2,7,8] but there is agreement that few tests are needed. This can be as simple as a complete blood cell count and a sedimentation rate or C-reactive protein measurement. Even those are debatable, but high eosinophil counts might trigger a stool examination for ova and parasites. Routine skin testing for food allergy is not recommended.[2,7,8] There is a clear association of CSU with autoimmune disorders, such as Hashimoto thyroiditis[9,10]; however, although 25% of patients may have elevated antithyroid antibodies, such as antithyroperoxidase or antithyroglobulin,[11] most have normal thyroid function (total thyroxine and thyrotropin). Thus, routine evaluation for the presence of thyroid abnormalities is not recommended by some guidelines[7,8] but is included in others.[2,12] Although patients with systemic lupus erythematosus (SLE) can have urticaria, the incidence of SLE in patients presenting with CSU is extremely low. However, the incidence of a positive antinuclear antibody test (ANA) result is 15% to 30% (29% with titer exceeding 1:160 in a study by Viswanathan et al[13]) and typically leads to many additional laboratory tests, which prove to have negative results. A screening ANA is not recommended in the absence of symptoms (other than urticaria) that might suggest the presence of SLE even though both disorders are common in young women.

Pathogenesis

A detailed review of the pathogenesis of CSU has been published previously.[14] The major findings can be summarized as follows. First, the histologic features of the disease resemble an allergic late-phase response except the prominence of T_H2-type lymphocytes is not seen and the relative percentage of neutrophils and monocytes seems greater.[15,16] Second, there is an association of CSU with autoimmunity in approximately 45% of patients, but there are opinions for both pro[14,17] and con[18] to consider it an autoimmune disorder. Third, there is also an abnormality of signal transduction in basophils of patients (particularly regarding phosphatases) that reverses when the urticaria remits.[19–21]

CSU differs from inducible urticarias (except delayed pressure) because a prominent nonnecrotizing perivascular infiltrate is seen in CSU that is not evident in the other inducible urticarias.[22] The latter group is explicable largely by mast cell secretion of vasoactive mediators, predominantly histamine, which may relate to the more indurated feel and protracted duration of the urticaria in CSU in contrast to the fleeting lesions of the inducible urticarias. The lesions of CSU consist mainly of T lymphocytes (virtually no B cells) of T_H0 or mixed T_H1 and T_H2 subtypes, eosinophils, monocytes, and basophils.[16,23] The more recently described subpopulations of T lymphocytes such as T_H17, T_H22, T_H9, and natural-killer T cells have not been assessed.

There is an association of CSU with thyroid disease (mainly Hashimoto thyroiditis) but to a lesser degree with Graves disease, type 1 diabetes mellitus, Sjögren syndrome, and vitiligo.[24] The incidence of antithyroid antibodies is 25%[11] regardless of thyroid status consisting mainly of IgG antibody, but IgE antithyroperoxidase has been described as well.[25] Although the incidence of a weekly positive ANA test result is also high,[13] anti-DNA test results are typically negative. There is a 25% to 40% incidence of IgG antibody to the α-subunit of the IgE receptor, depending on the study,[26–28] and these antibodies are functional and provide a mechanism not only for histamine release from basophils, the cell most commonly assessed, but also from cutaneous mast cells.[29] Serum factors, particularly complement, augments the basophil histamine release,[30] and this has been demonstrated to be due to liberation of C5a.[31] For example, depleting sera of C5 or adding an antibody to the basophil C5a receptor inhibits complement-dependent augmentation of IgG-dependent histamine release, whereas fractionation of the IgG reveals a predominance of IgG anti-FcεRI in subclasses IgG_1 and IgG_3, which readily fix complement (in contrast to IgG_2 and IgG_4) when bound to antigen.[32] Also of theoretical interest is that saturating all of the α-subunits with monoclonal IgE obtained from a patient with an IgE myeloma inhibits the ability of the IgG anti-IgE receptor to release histamine, indicating that in most instances the antibody interacts with unoccupied IgE receptors and that the ability of the antibody to cross-link IgE receptors is requisite for histamine release as it is for antigen cross-linking of cell-bound IgE in allergic reactions.[33] In addition, 5% to 10% of patients have IgG anti-IgE antibodies apart

from IgG anti-IgE receptor antibodies and that these are functionally indistinguishable from antireceptor antibody.[34,35] Stripping IgE from the surface of basophils eliminates the effect of IgG anti-IgE while adding a myeloma IgE to saturate receptors augments IgG anti-IgE while it inhibits antireceptor antibody.[26]

The counterconsiderations are as follows. Approximately 55% of patients lack these antibodies. Thus, if autoimmunity provides a pathogenic mechanism for activation of cutaneous mast cells in CSU, it is only identifiable in a subpopulation of patients. Although there have been reports of the presence of such antibodies in healthy individuals[36] or in those with urticaria other than CSU,[37,38] it seems clear that the incidence is far less than is seen in CSU. These antibodies are not reported in patients with atopic disorders, such as allergic rhinitis, asthma, or atopic dermatitis. There are 2 studies that report such antibodies in patients with connective tissue diseases. In the first study, antibodies binding to the α-subunit of the IgE receptor was reported in many autoimmune diseases, such as SLE and dermatomyositis, but these appeared nonfunctional (ie, they did not cause histamine release),[39] whereas the only functional antibodies were in patients with CSU. The second study, however, found functional antibodies with this specificity in CSU (highest percentage) and SLE[40] patients, although it was uncommon in other controls. However, the patients with SLE did not have urticaria. Another issue is the identification of binding antibody to the α-subunit, typically done by enzyme-linked immunosorbent assay[21,37] vs functional antibody by basophil histamine release. The fact that binding antibody has not correlated with histamine release or clinical urticaria has led to concern that the IgG antireceptor antibody is an epiphenomenon.[8] Although there is no correlation of binding antibody with basophil histamine release,[30–32] basophil histamine release had an unequivocal association with the presence of CSU,[41] even considering the exceptions noted above. The reason for this discrepancy is not yet clear, but the presence of anticarbohydrate antibody in patients' serum cross-reactive with the insect vector carbohydrate attached to the cloned α-subunit being used in the enzyme-linked immunosorbent assay is suspected.[42] The effect on histamine release is marginal, if at all, but this observation may invalidate all binding methods that use this antigen.

None of the current guidelines include determination of anti-IgE or anti-IgE receptor antibodies as part of their recommended evaluation of patients with CSU. These antibodies are of obvious theoretical interest, but none of the treatment modalities distinguish patients with the antibodies from those without them. The exclusion of a thyroid evaluation in patients with CSU is questionable because so many patients are found to be hypothyroid based on their total thyroxine and thyrotropin levels and are then treated with a thyroid hormone. A prospective study of the percentage of new patients with CSU who are hypothyroid, thyroid antibodies notwithstanding, would be helpful.

Because routine determination of anti-IgE receptor antibodies is not included in current guidelines, one consideration is performance of the autologous skin test. I mention this only briefly because it has historical significance and is prominent in the literature. Serum is obtained from the patient with CSU and injected into the patient's own skin; the result is considered positive if a significant wheal-and-flare reaction is noted compared with a buffer control.[43] This test generally (but not perfectly) reflects the presence of anti-IgE receptor antibody,[44] and a biopsy specimen of the induced lesion resembles the histologic features of an IgE-mediated late-phase reaction,[45] which is another point in favor of the potential pathogenicity of the autoantibodies. However, the test is time consuming and requires clotting blood and centrifuging under sterile conditions. The percentage positive is approximately 25% to 30% similar to the lower figures reported for serum-dependent basophil histamine release. The term *autoreactivity* has crept into the literature because every positive skin test result is not accompanied by a positive test result for antireceptor antibodies. This, unfortunately, makes the exception, the rule. The correlation with autoimmunity is high[46] and the focus need not be on the outliers. Studies seeking an explanation for the positive autologous skin test result in CSU are what led to the discovery of anti-FcεRI antibodies.[21,42]

Treatment

One would ideally like to see double-blind, placebo-controlled studies that involve large numbers of patients to make recommendations regarding therapy of CSU. However there are only a small number of medications whose assessment would be consistent with such criteria. Guidelines to assist in making a choice regarding therapy have been published[7,8,12,47] and attempts made to assess the confidence with which any recommendation can be made, depending on the quality of the evidence. To a large degree, personal experience still influences such recommendations because the studies to which one would ideally like to refer have not been performed.

There is uniform agreement that antihistamines should be tried first. It is of historical interest that the dose and choice of agent have often first been validated for one of the histamine-dependent physical urticarias. Subsequently, similar studies were performed using patients with CSU, and in each instance, the same result was obtained, although the incidence of antihistamine resistance is higher in CSU. Early on, the only antihistamines available were first-generation agents, such as diphenhydramine, hydroxyzine, cyproheptadine, pyribenzamine, and chlorpheniramine. One classic example is the use of cyproheptadine to treat cold urticaria,[48,49] where it was found that a dose of 4 mg taken 3 to 4 times a day was particularly effective. This approach was applied to other physical urticarias[50] and then to CSU. In the latter disorder, use of hydroxyzine at 50 mg 4 times per day maximized responsiveness to antihistamines.[51,52] When the next-generation antihistamines came to market they were advertised as being effective at once per day dosing and were relatively nonsedating. These antihistamines were effective for allergic rhinitis, but when patients with CSU were switched the first-generation agents to these newer antihistamines virtually everyone whose urticaria had been controlled then experienced exacerbation. At that time there were, of course, no generic preparations, and cost beyond 1 tablet per day was expensive with no insurance coverage, whereas first-generation agents were effective, inexpensive, and approved at 3 to 4 times per day.[52] Numerous articles that appeared during the next phase of development pointed out the adverse effects of first-generation antihistamines, including sedation, dryness, poor concentration, and poor performance during challenge tests[53–56]; however, these antihistamines were still recommended. It was demonstrated that first-generation agents readily crossed the blood-brain barrier.[56] whereas the newer agents did so far less or not at all. Although true, there are some general faults with such studies. First, the patient population was virtually never patients with chronic urticaria. The drugs were tested in healthy volunteers or patients with other allergic disorders and the results extrapolated to CSU. Second, the doses tested were single (typically 50 mg of diphenhydramine) for a short interval. Experience treating thousands of patients with CSU suggested that tolerance to the sedation wore off in a week, which is important because the medication is taken prophylactically for months or even years and there was no evidence of dose response (ie, adverse effects with higher doses were not proportionately greater than was seen with lower doses).[57] Third, pruritus was controlled, patients slept better, and the positive effects appeared to outweigh the negative. Because such observations were anecdotal, a major criticism is that patients report subjective

symptoms and formal testing might still reveal abnormal functioning.

This issue has been resolved but in an unanticipated manner. It was found that either levocetirizine or desloratadine taken 4 times a day for cold urticaria is optimal[58] and that proportionally greater control was obtained as one advanced from 1 tablet per day up to 4 tablets per day. Next the same approach was used for patients with CSU[59] with similar success. Thus, high-dose antihistaminics as a therapy for persisting urticaria, regardless of type, an observation that is at least 35 years old, was validated. In the United States, a variety of second-generation antihistamines became available as generic preparations, some of which are available over the counter at a low cost so insurance coverage is not an issue. Thus, there is no reason to use first-generation antihistamines to treat any form of persisting urticaria, and all guidelines emphasize starting with nonsedating antihistamines.

Nevertheless, the emphasis of adverse effects of first-generation agents when prescribed to patients with CSU appears exaggerated. This revision is supported by a meta-analysis that failed to observe a major difference in adverse effects[60] and a recent study of antihistamine use in children with food allergies[61] in which the anticipated differences in adverse effects of first-generation vs second-generation antihistamines was not seen. The first generation-agents indeed had a higher incidence of adverse effects, but the difference between them was surprisingly small and did not reach statistical significance. In addition, the increment between them would likely lessen if the duration had been longer.

Approximately 45% of patients with CSU are adequately treated with antihistamines, yet 55% are relatively insensitive or completely refractory. Guidelines often approach this as a stepwise procedure, and the second step can be addition of either a histamine$_2$ (H_2)–receptor antagonist[8] or a leukotriene antagonist.[7] However, it was pointed out that the evidence of efficacy of each in the treatment of CSU was relatively weak[7,8] but with an excellent adverse effect profile. In the most recent guideline of the European Academy of Allergy and. Clinical Immunology and the World Allergy Organization, H_2-receptor antagonists were eliminated, whereas guidelines promulgated by the American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology in the United States retained them. My own view regarding these drugs has evolved. Although I used both routinely along with H_1-receptor antagonists (often simultaneously rather than using them stepwise) in recent years, I advocated eliminating both[57] in part because the evidence favoring leukotriene antagonists used either alone or in combination with H_1-antihistaminics[62,63] was balanced by the evidence demonstrating a lack of efficacy.[64,65]

Step 3 agents to be used are often listed but not recommended in any particular order (Table 1). Given the listing of those where the evidence favoring efficacy for CSU is limited, the one most commonly used is corticosteroid. There is not one guideline that favors their use except for short tapering courses (eg, 3-10 days) to control severe exacerbations because cumulative adverse effects are truly prohibitive.[7,8] Before the advent of cyclosporine and omalizumab, for which efficacy is in the 60% to 70% range for otherwise refractory patients,[66,67] I too used corticosteroids in the long term because severe CSU could be unresponsive to every other agent on this list and to try them all in succession was a lesson in frustration for everyone. The key to success was to limit the dose to a maximum of 20 mg every other day or, later on, 10 to 12 mg daily but with a gradual decreasing dose that was ultimately eliminated. I believed that overuse of steroid was the most prominent error in the treatment of CSU and that the second most prominent error was avoiding using them completely. Cyclosporine and omalizumab have limited my use of corticosteroid to severe acute exacerbations according to current guidelines. The same argument for their use or nonuse in rheumatoid arthritis (in the 5- to 10-mg/d range) has gone on for at least 40 years[68,69] and is not resolved.

Table 1
Therapy for chronic spontaneous urticaria

Step	Therapy
1[a]	Nonsedating, second- or third-generation antihistamines taken 4 times a day. Decrease the dose as tolerated once control of symptoms is attained. If response inadequate, proceed to step 2.
2	Omalizumab, 300 mg monthly. If no response after 2 injections, proceed to step 3.
3	Cyclosporine, 200-300 mg/d
4[b]	Options to consider if steps 1-3 fail: dapsone, methotrexate, sulfasalazine, hydroxychloroquine, intravenous γ-globulin, and plasmapheresis.

[a]Dose of cetirizine, loratadine, desloratadine, or levocetirizine corresponding to hydroxyzine or diphenhydramine at 50 mg 4 times daily is 6 tablets per day.
[b]Expected response rate based on the literature. Patient response to step 1 was 45%. Patient response to step 2 was 65% of the remainder. Calculated response rate of steps 1 plus 2 was 81%. Patient response to step 3 was 65% of the remainder. Calculated total response rate for steps 1, 2, and 3 was 92%.

Dapsone, hydroxychloroquine, sulfasalazine, colchicine, methotrexate, intravenous γ-globulin, and plasmapheresis have all been used to treat CSU; some initially were drugs used in the treatment of cutaneous vasculitis and/or urticarial vasculitis and were assumed to be equally effective for CSU. That is not the case. Further, there is virtually no double-blind, placebo-controlled study of any of these agents with a success rate significantly higher than 30% (the rate of success with placebo); thus, their recommendation stems from relatively small trials of brief duration, some with no control group. Some of the studies note a response a few months after use of the drug is instituted, which is suspect (Table 2).

Hydroxychloroquine may have particular efficacy for the hypocomplementemic urticarial vasculitis syndrome,[70] but its utility in CSU is based on one study[71] that was underpowered to allow any conclusion.[8] There are few reports recommending colchicine[72] or dapsone[73,74] or sulfasalazine,[75,76] but all are believed to be reasonable choices for neutrophilic CSU[77] (ie, a CSU patient whose skin biopsy specimen reveals a particular prominence of neutrophils with refractoriness to antihistaminics and possibly corticosteroids as well). Neutrophils are present in most biopsy specimens of patients with CSU,[78] although the percentage can vary greatly, and a skin biopsy is no longer recommended as part of the evaluation for CSU unless urticarial vasculitis is suspected.[7,8] Examples of circumstances where a skin biopsy should be performed would be the presence of fever, concomitant petechiae or palpable purpura, lesions that fade with bruising, individual lesions lasting longer than 24 hours (and certainly longer 36 hours), or prominent arthralgia. An ANA, C3, C4, and C1q binding assay for circulating immune complexes and cryoglobulin determination would be among the tests that would be included. However, there are far

Table 2
Approaches to consider when antihistaminic therapy fails

Recommended[a]	Consider if previous therapy fails	No recommended
Omalizumab Cyclosporine	Dapsone Hydroxychloroquine Sulfasalazine Colchicine Methotrexate Intravenous γ-globulin Plasmapheresis	Corticosteroid[b] Histamine$_2$-receptor antagonists Leukotriene antagonists

[a]Recommended because of high percentage response rate.
[b]Failure of antihistaminics, omalizumab, and cyclosporine may leave no option other than those listed in the second column or use of a low-dose, long-term corticosteroid with the provisos described in the text.

more studies of colchicine, hydroxychloroquine, and dapsone that report success in treated urticaria with vasculitis compared with CSU, and the few articles referenced above are not double-blind, placebo-controlled studies.

Intravenous γ-globulin appears to be effective in an unknown percentage of patients but requires monthly intravenous administration,[79,80] and these reports lack any control group. Methotrexate is relatively easy to use (orally or intramuscularly), and there is a large experience in its use for rheumatoid arthritis, but we really do not know the success rate for CSU, and its use is based largely on case reports.[81] The efficacy of plasmapheresis[82] in those with autoantibodies to the IgE receptor is, perhaps, the best evidence of possible pathogenicity; however, one would need to demonstrate removal of particular autoantibodies and use patients lacking autoantibodies as a control group.

Cyclosporine, however, fulfills most criteria for an immunosuppressive agent that is effective in CSU, including patients unresponsive to antihistamines and who might otherwise be receiving repeated courses of corticosteroids. It is also among the only immunosuppressive drugs that inhibit histamine release from human basophils[83] or skin mast cells.[84] Two double-blind, placebo-controlled studies initially demonstrated efficacy,[85,86] with a response rate of 60% to 80%,[66] often with complete clearing of urticaria. The effect is typically evident within a week. There is significant toxicity associated with cyclosporine use, including an increase in blood pressure and a decrease in renal function, and in 120 patients studied, 20 discontinued use of the drug because of adverse effects. One hundred patients were maintained with long-term therapy. Cyclosporine is contraindicated in patients who present with hypertension or compromised renal function. It is recommended that patients have a blood urea nitrogen, creatinine, urinalysis, and blood pressure check at the onset, which is repeated at 4- to 6-week intervals. My experience has been occasional adverse effects with increasing blood pressure, blood urea nitrogen level, or creatinine level (eg, an increase in creatinine level from 0.91 to as high as 2.2 mg/dL). Use of the drug was discontinued, and all patients' renal function reverted to normal within 4 to 6 weeks. An increase in blood pressure was less common, but when present use of the drug was discontinued. In only one instance was blood pressure treated with continued cyclosporine to keep it in the reference range, although use of cyclosporine was ultimately discontinued when the urticaria remitted. Subsequent publications document the efficacy of cyclosporine in an additional 68 adult patients,[87] and success was also reported in children.[88] Anecdotal reports from physicians experienced in its use attest to the fact that none of the other drugs used to treat CSU (ie, dapsone, hydroxychloroquine, sulfasalazine, colchicine, methotrexate, and intravenous γ-globulin) can match the results seen with cyclosporine. Thus, although all guidelines suggest that some of these be tried before cyclosporine, the response rate of any of them is significantly lower than that of cyclosporine; thus, a drug with clear efficacy and manageable adverse effects should be used first.

Nevertheless, there is no medication that produces the results seen with omalizumab given efficacy equal to or better than that seen with cyclosporine with few adverse effects. Initially, case reports of success with its use in chronic urticaria[89] or idiopathic angioedema[90] were reported, as well as the first controlled study of 12 refractory patients.[91] The later study was single-blinded, and each patient received both placebo and drug in an order that was unknown to the patient. It was administered subcutaneously monthly based on the patient's weight and IgE level following the protocol for its administration for asthma. Seven patients had complete disease remission, 4 patients improved significantly, and 1 did not respond. This was followed by a dose-ranging, double-blind, placebo-controlled study of 82 patients showing similar efficacy with no significant adverse effects. A dose of 300 mg monthly appeared optimal.[92] A second phase 2 study focusing on patients with antithyroperoxidase antibodies again revealed efficacy of more than 60% (meaning virtually no urticaria whatsoever) often with remarkable responses (eg, no urticaria within 2-3 days of receipt of the first injection).[93] This has been followed by 3 phase 3 studies, 2 of which have been previously published.[67,94] The first of these studies involved 323 patients with moderate-to-severe CSU receiving a licensed or approved dose of a second-generation H_1-antihistamine. Significant improvement on administration of omalizumab monthly for 3 doses (12 weeks) was noted in 66% of patients receiving the 300-mg dose compared with 19% with placebo, and 44% were completely hive free. Efficacy was dose dependent, with the 300-mg dose demonstrating greater efficacy[90] than the 150-mg dose. The second study extended the duration to 24 weeks and allowed therapy with up to 4 times the approved dose of a second-generation antihistamine plus either an H_2-antihistamine, a leukotriene antagonist, or both. This was meant to resemble a clinical practice where all of these drugs may be prescribed without significant or adequate control of symptoms. A total of 252 patients were enrolled plus control subjects. The results were strikingly similar to those reported previously, with significant improvement in weekly urticaria score, size of largest lesions, time to achieve a response, angioedema-free days, pruritus, and hive-free days. Adverse events did not differ from the placebo arm. Once therapy was discontinued, symptoms gradually increased back to the placebo level. The overall response rate was 52% at week 12, and the percentage of patients who became hive free was 34%.

The mechanism of action of omalizumab in chronic urticaria is not known. Originally, the idea was that by lowering IgE levels we would secondarily lower IgE receptor density on the surface of the mast cells (or basophils) and that IgG antireceptor antibodies would be unable to cross-link cell surface receptors so that the cells would not activate.[91] However, the drug is equally effective in those lacking autoantibodies,[67,92,94,95] and urticaria can cease in some within 1 to 3 days, far too rapidly to invoke receptor down-regulation. In addition, patients receiving omalizumab have been reported to have increased sensitivity to agonists acting through the IgE receptor with basophil secretion enhanced at a time that urticaria has ceased.[96] This paradox leaves open any idea regarding mechanism of action but refocuses attention to the cutaneous mast cell rather than the blood basophil, where receptor down-regulation leads to decreased mediator release, although the timing of the effect is slower than therapeutic effects observed in vivo.[97] The presence of IgE antibody to an unknown autoantigen or intrinsically abnormal IgE should be considered.

Conclusion

Because of the striking response of patients to omalizumab and safety considerations, an approach to therapy that uses omalizumab much earlier than guidelines recently (or about to be) published may be necessary. There is general agreement that second-generation antihistamines up to 4 times the dose typically recommended for allergic rhinitis should be used first. The anticipated response rate is 45%. At that dose, there is no evidence that addition of an H_2-antihistamine or leukotriene antagonist would add anything; therefore, this step can be skipped. If omalizumab were to become the next choice, an additional 65% response rate is expected. Thus, 65% of the remaining 55% is an additional 36% for a combined response rate of 81%. The remaining 19% are refractory patients who will be difficult to treat. In this circumstance, cyclosporine will yield the highest success rate, perhaps another 60% of the remainder for a total response rate of 92%. Others might try dapsone or sulfasalazine or methotrexate as alternatives to cyclosporine. However, dapsone has significant toxicity,[98] and more studies are needed to assess the effects of sulfasalazine or

methotrexate. For the 8% or so of patients in whom antihistamine, omalizumab, and cyclosporine fail, sulfasalazine or methotrexate should be considered. When one reaches this scenario, however, low-dose steroids starting at 10 to 15 mg daily and tapering by 1 mg per week can be particularly helpful.[51,56]

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